Practical Management of the GYN-Oncology Patient Discussing Real Life Cases

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Case 1

M.P, 58 years old woman, with history of controlled hypertension, complained in 02/2013 of abdominal bloating and dyspnea. After CT-scan, pleural stage IV ovarian cancer is suspected.

- Laparoscopy suggested that complete peritoneal resection was possible and she underwent laparotomy, bilateral salpingo-oophorectomy, total hysterectomy, peritoneal diaphragmatic and Douglas pouch stripping, omentectomy and peritoneal debulking.
- Histology: Endometrioid grade 2
- Residuals lesions < 1 cm were left on the mesentery

Questions

- **Which chemotherapy to choose ?**
- **What is the optimal length of Bev administration?**
- **What is the optimal Dosage of Bev?**
- **IV or IP?**
- **What about the combination of BEV with an anti-PARP (olaparib)?**

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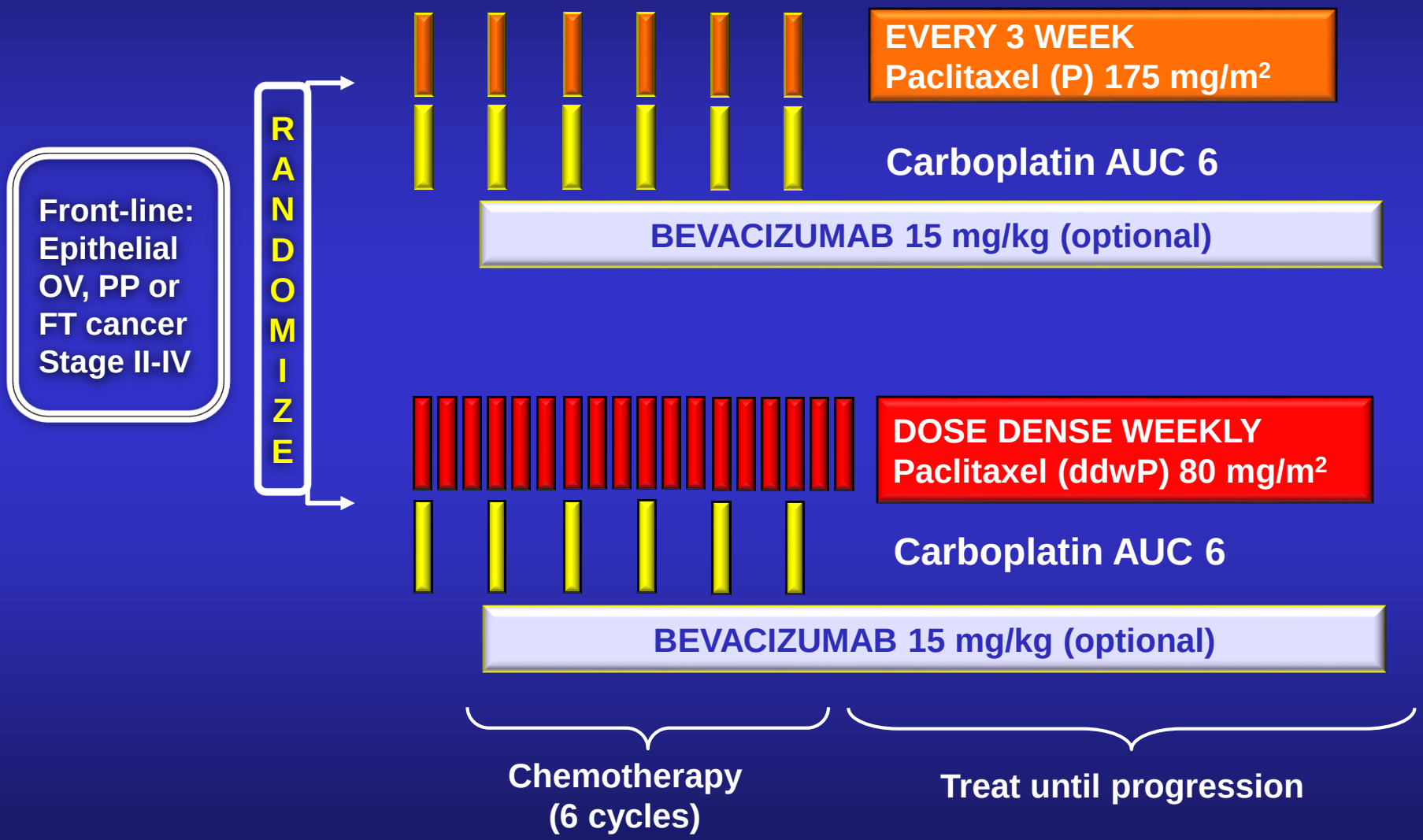
GOG-262: modifying dose regimen schema



GOG-262: Clinical Characteristics (n=692)

Characteristic		total	Arm I PC +/- BEV (n=346)	Arm II ddwPC +/- BEV (n=346)
Stage	II	18	10 (3%)	8 (2%)
	III	472	229 (66%)	243 (70%)
	IV	202	107 (31%)	95 (27%)
Site of origin	Ovary	550	281 (81%)	269 (78%)
	Fallopian tube	68	32 (9%)	36 (10%)
	peritoneum	74	33 (9%)	41 (12%)
Size of Residual	Microscopic	167	83 (24%)	84 (24%)
	Gross	437	219 (63%)	218 (63%)
	Neo-adjuvant	88	44 (13%)	44 (13%)

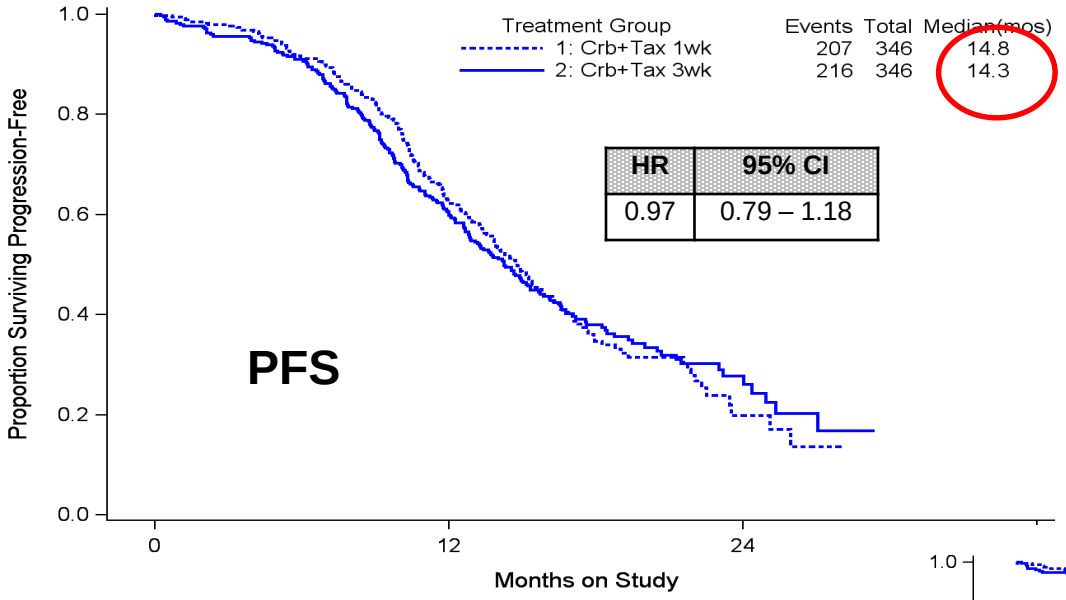
Percentages may not total 100% due to rounding or categorization

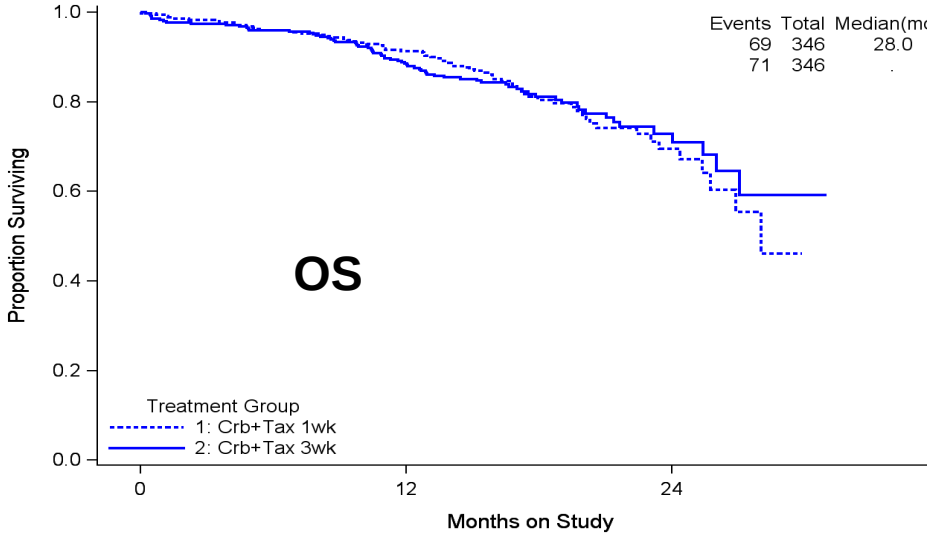
Upfront ovarian cancer treatment - modifying dose regimen

GOG-262: Adverse Events

Adverse event n (%)	Arm I PC +/- BEV (n=343)	Arm II ddwPC +/- BEV (n=340)	p value
Anemia (grade ≥3)	54 (15.7%)	**124 (40.8%)**	p<0.001
Neutropenia (grade ≥3)	**285 (83.1%)**	245 (72.0%)	p<0.001
Febrile neutropenia	16 (4.7%)	13 (3.8%)	p=0.72
Sensory neuropathy (grade ≥2)	61 (17.8%)	**88 (25.9%)**	p=0.012
GI events (grade ≥2)	15 (4.4%)	24 (7.1%)	p=NS
Vascular disorders (grade ≥3)	56 (16%)	60 (18%)	p=NS
Renal / urinary (grade ≥3)	19 (6%)	17 (5%)	p=NS

GOG-262


Treatment Group
1: Crb+Tax 1wk
2: Crb+Tax 3wk
Events Total Median(mos)
207 346 14.8
216 346 14.3
HR 95% CI
0.97 0.79 – 1.18
PFS
Proportion Surviving Progression-Free
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
Months on Study


Events Total Median(mo
69 346 28.0
71 346 .
OS
Proportion Surviving
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0.8
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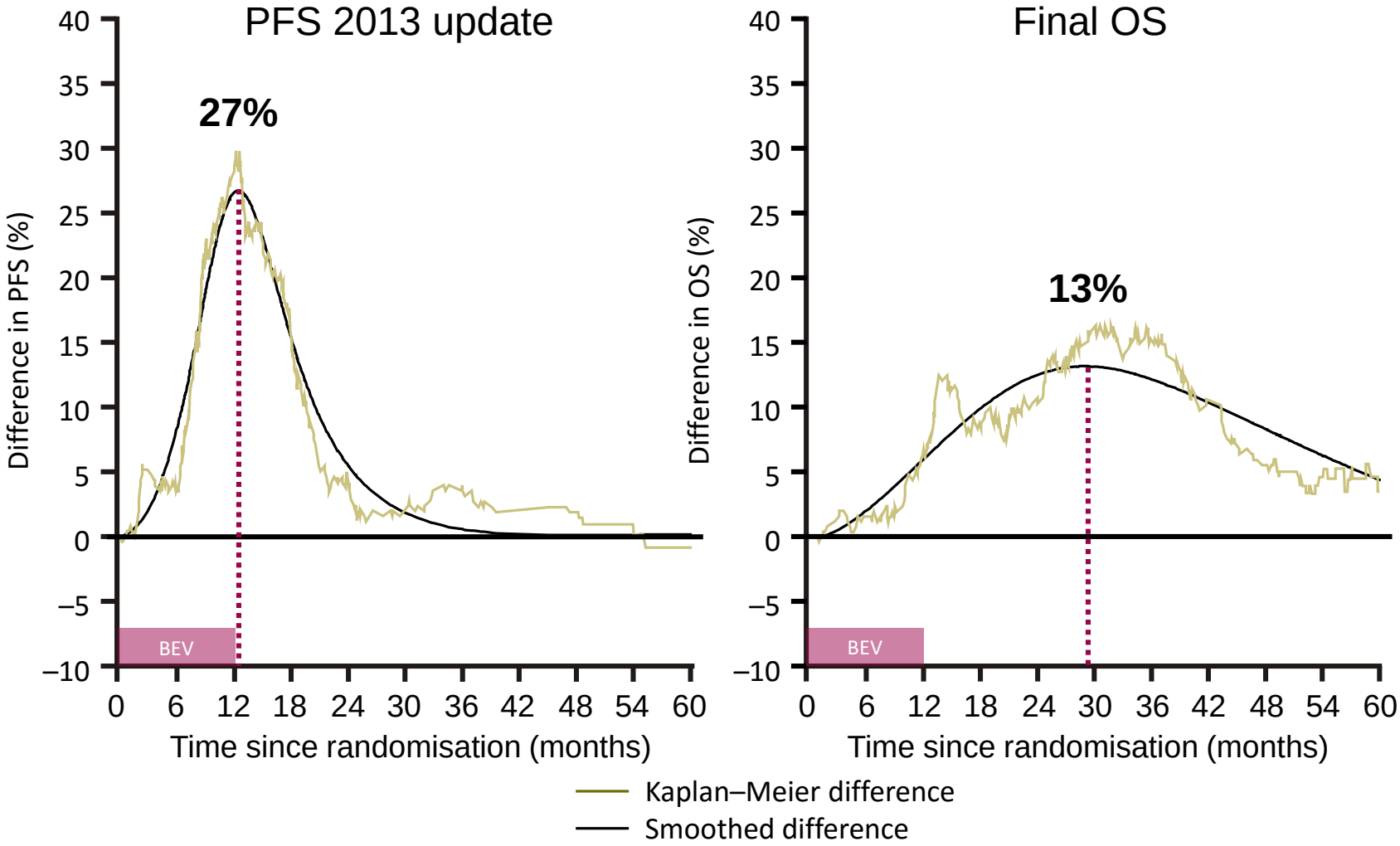
Absolute difference in PFS and OS: High-risk subgroup



Primary results from ROSiA, a single-arm study evaluating extended duration of bevacizumab combined with front-line carboplatin and paclitaxel for epithelial ovarian cancer

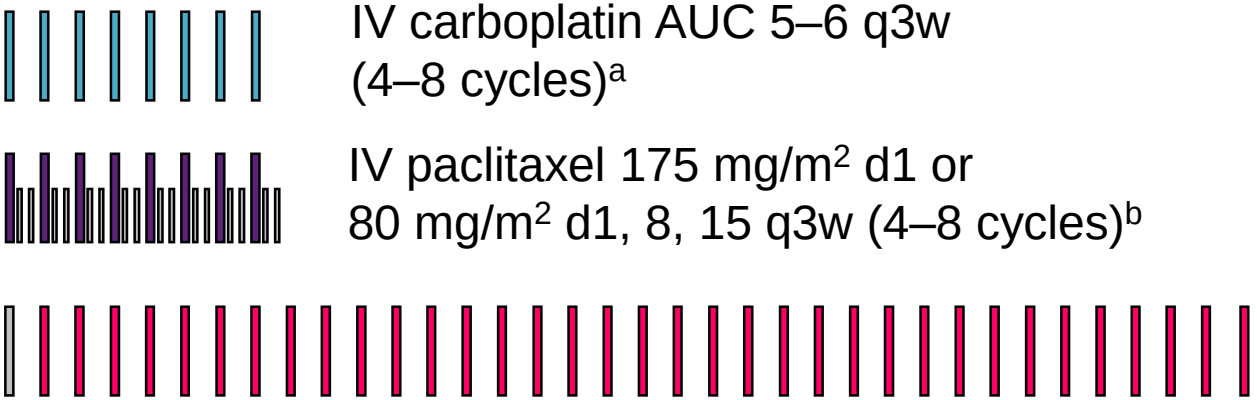
N Colombo[1], I Davidenko[2], J Korach[3], C Mendiola[4], F Selle[5], P Ghatage[6], S Ottesen[7], HYS Ngan[8], U De Giorgi[9], C Alberto Hernandez[10], LH Wei[11], CM Chuang[12], HH Chou[13], N Martin[14], S Robb[14], I Dolado[15], AM Oza[16]

[1]European Institute of Oncology and University of Milan Bicocca, Milan, Italy; [2]Clinical Oncology Dispensary #1, Krasnodar Region Ministry of Healthcare, Krasnodar, Russia; [3]Sheba Medical Center, Tel Hashomer, Israel; [4]University Hospital 12 de Octubre, Madrid, Spain; [5]Tenon Hospital AP-HP and Alliance Pour la Recherche en Cancérologie, Paris, France; [6]Tom Baker Cancer Centre, Calgary, AB, Canada; [7]Roskilde Sygehus, Roskilde, Denmark; [8]Queen Mary Hospital, University of Hong Kong, Hong Kong, Hong Kong; [9]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Istituto Di Ricovero e Cura a Carattere Scientifico (IRST IRCCS), Meldola, Italy; [10]Oaxaca Site Management Organization, Oaxaca, Mexico; [11]National Taiwan University Hospital, Taipei City, Taiwan; [12]Taipei Veterans General Hospital, Taipei City, Taiwan; [13]Linkou Chang Gung Memorial Hospital, Taipei City, Taiwan; [14]F Hoffmann-La Roche Ltd, Basel, Switzerland; [15]Hays AG, Basel, on behalf of F Hoffmann-La Roche, Global Medical Affairs, Basel, Switzerland; [16]Princess Margaret Hospital, University of Toronto, Toronto, ON, Canada

Study design

- **Epithelial ovarian, fallopian tube or primary peritoneal cancer:**
  - Stage IIB–IV
  - Grade 3 stage I/IIA
  - Clear-cell carcinoma (any stage)
  - Carcinosarcoma
- **Maximally debulked (prior neoadjuvant chemotherapy allowed)**
- **ECOG PS 0–2**

Dec 2010–May 2012:
1021 patients enrolled



Patients without progression at cycle 36 could continue therapy after discussion with the Steering Committee

- Primary endpoint: Safety (AEs by NCI-CTCAE version 4.03)
- Secondary endpoints: PFS, ORR, duration of response, overall survival
- Exploratory objectives: Optional translational research

[a]Cisplatin permitted in patients with hypersensitivity to carboplatin
[b]A change from one paclitaxel regimen to the alternative during the study was not permitted
ECOG PS = Eastern Cooperative Oncology Group performance status; ORR = overall response rate

ROSiA

Baseline characteristics (N=1021)

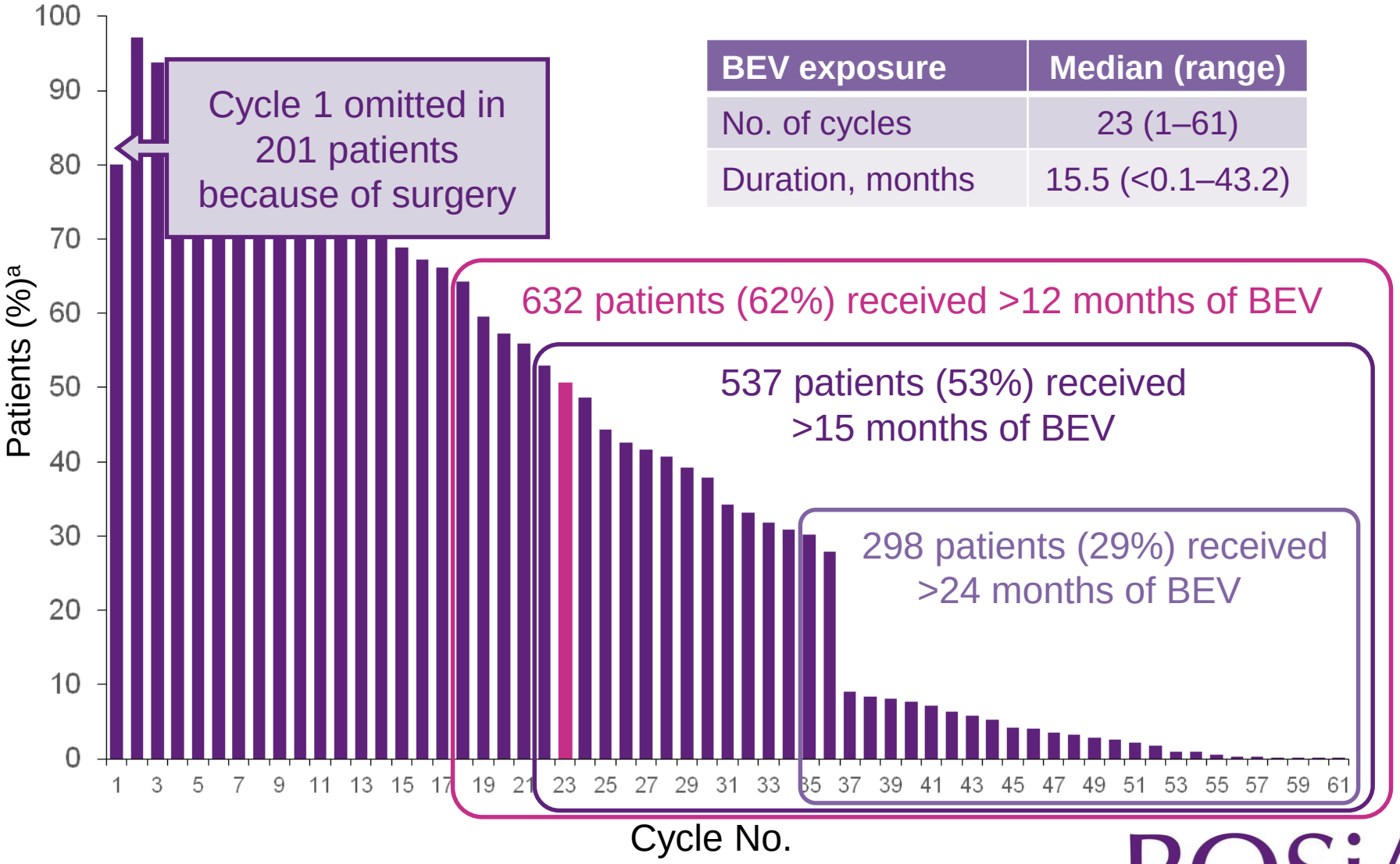
Characteristic		No. of patients (%)
Age at screening, years	Median (range)	56 (20–82)
	≥70 years	121 (11.9)
ECOG PS[a]	0	706 (69.1)
	1/2	307 (30.1)
Hypertension at baseline		336 (32.9)
FIGO stage	I/II	167 (16.4)
	III (not further classified)	29 (2.8)
	IIIA	40 (3.9)
	IIIB	60 (5.9)
	IIIC	485 (47.5)
	IV	240 (23.5)
Outcome of debulking surgery (N=967)[b]	>1 cm	328 (33.9)
	≤1 cm	639 (66.1)
	Macroscopic (1–10 mm)	200 (20.7)
	Microscopic (<1 mm)	286 (29.6)
	Unknown/missing	153 (15.8)
High risk (MRC definition)[c]		468 (45.8)

23%

[a]Missing in 8 patients (0.8%). [b]Percentages calculated using a denominator of 967 (patients with debulking surgery). [c]FIGO stage III and >1 cm residual disease or any FIGO stage IV or no debulking surgery
MRC = Medical Research Council

ROSiA

Bevacizumab exposure by cycle



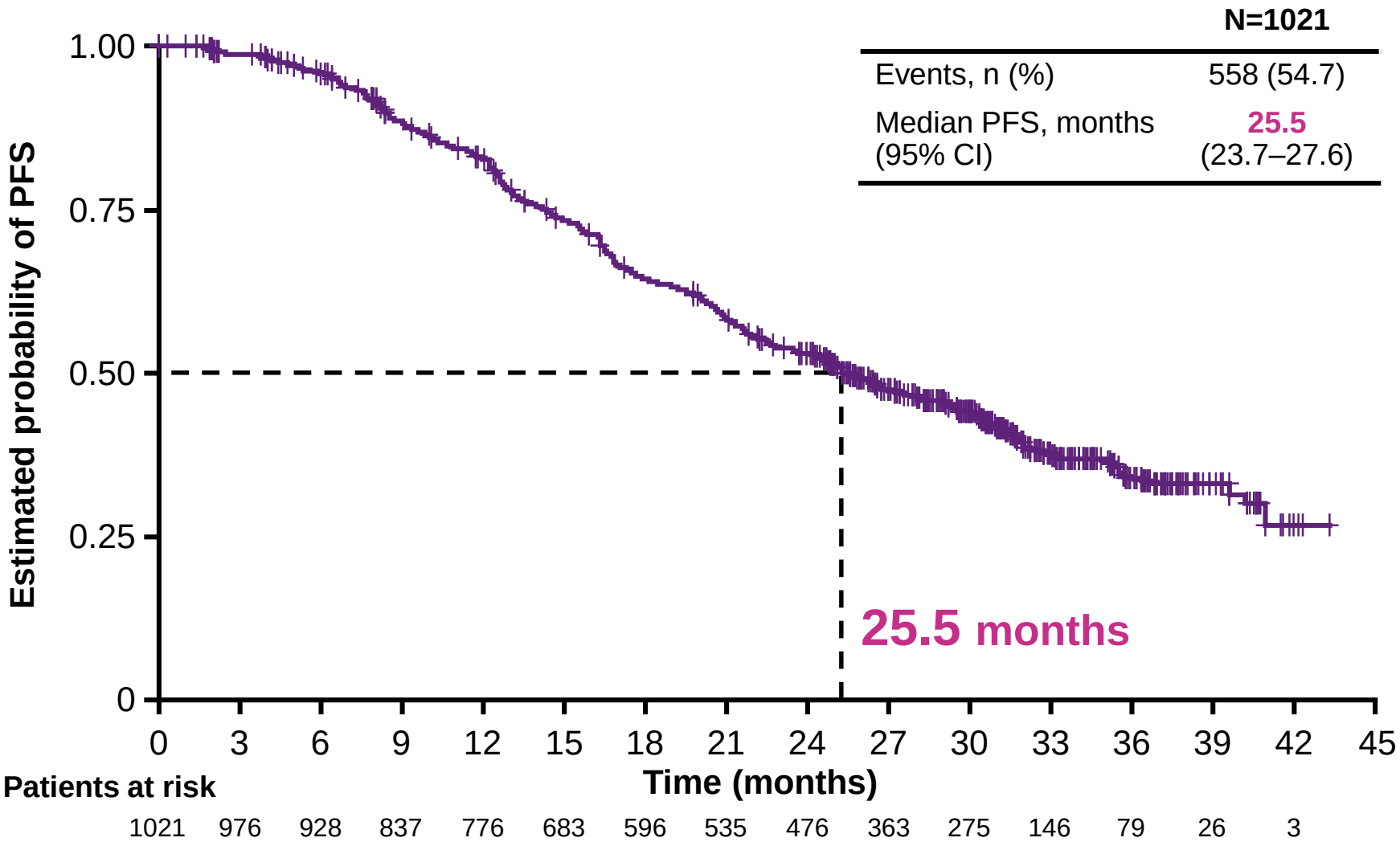
BEV exposure	Median (range)
No. of cycles	23 (1–61)
Duration, months	15.5 (<0.1–43.2)

[a]Denominator at each cycle is 1021

ROSiA

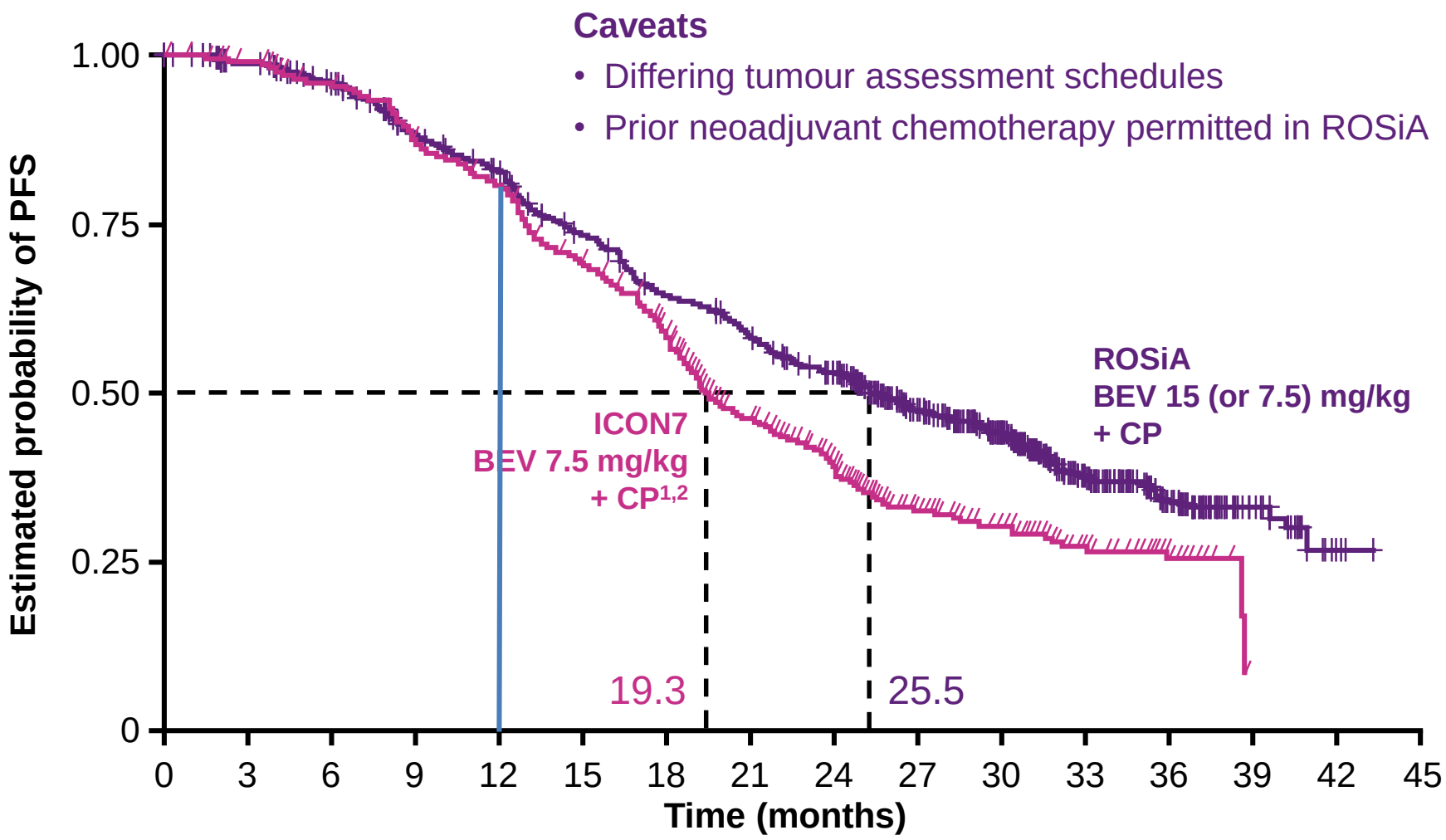
Progression-free survival (ITT population)

Median duration of follow-up: 32.0 months (range 0.7–49.5 months)



Data cut-off: 7 Dec 2014. ITT = intent-to-treat

PFS in ROSiA and ICON7 (ITT populations)

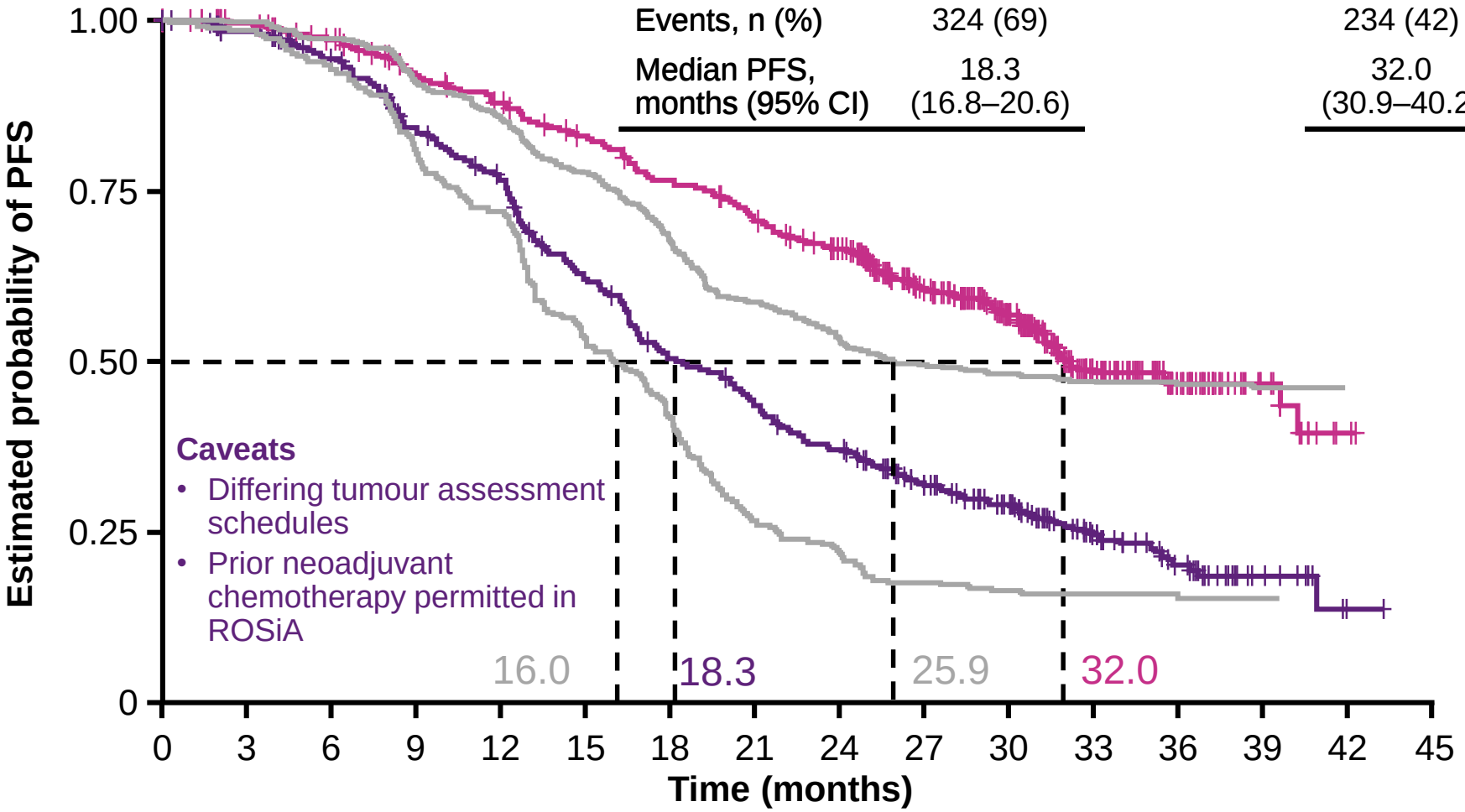


CP = carboplatin + paclitaxel

[1]Avastin SmPC;
[2]Roche data on file 2012 (ICON7 CSR addendum).

PFS in ROSiA and ICON7 according to 'MRC' risk status

PFS	High risk[a] (N=468)	Non-high risk (N=553)
Events, n (%)	324 (69)	234 (42)
Median PFS, months (95% CI)	18.3 (16.8–20.6)	32.0 (30.9–40.2)



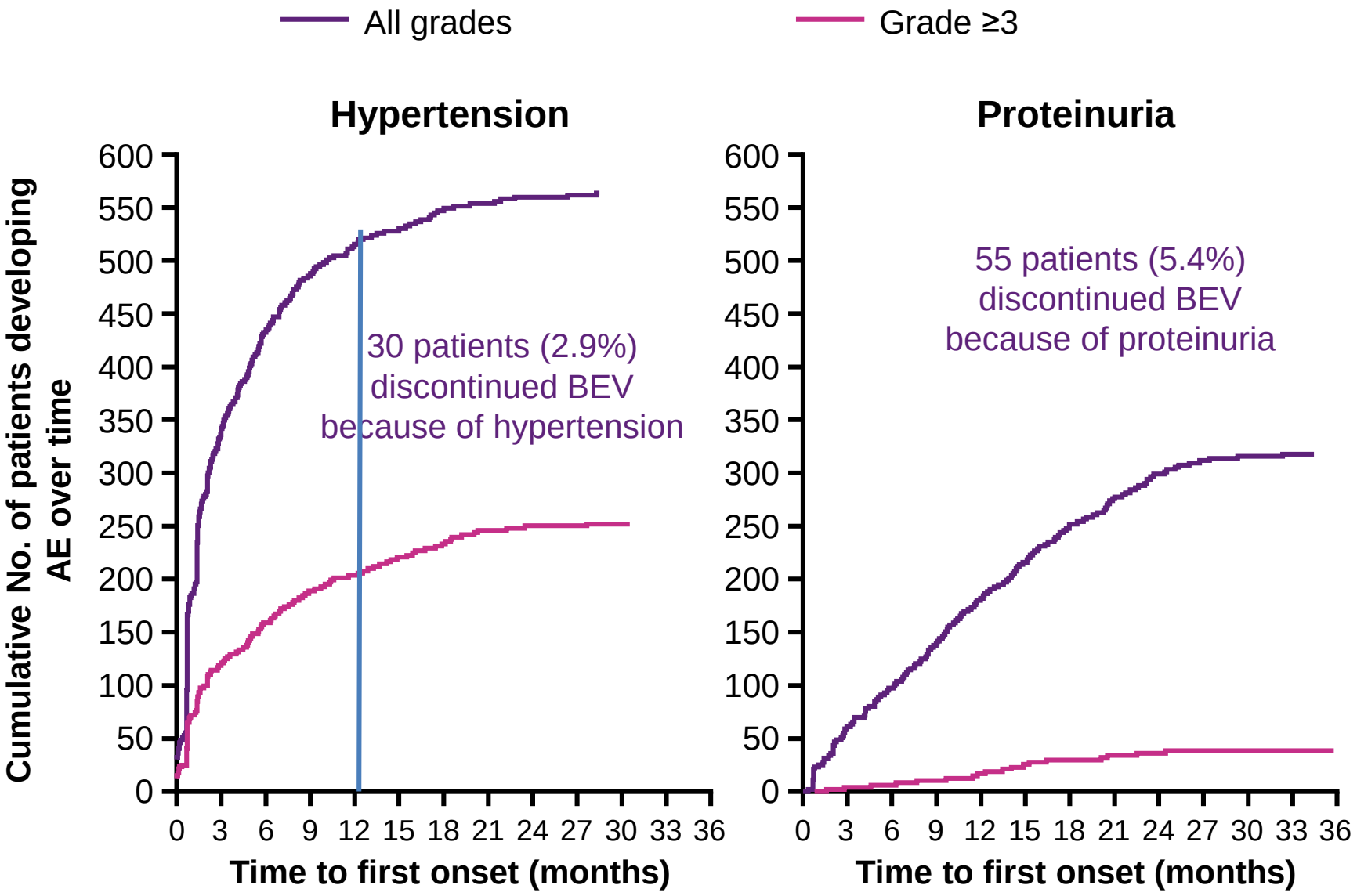
NE = not estimable

[a]FIGO stage III and >1 cm residual disease or any FIGO stage IV or no debulking surgery.

[1]Gonzalez-Martin A, et al. ASCO 2015

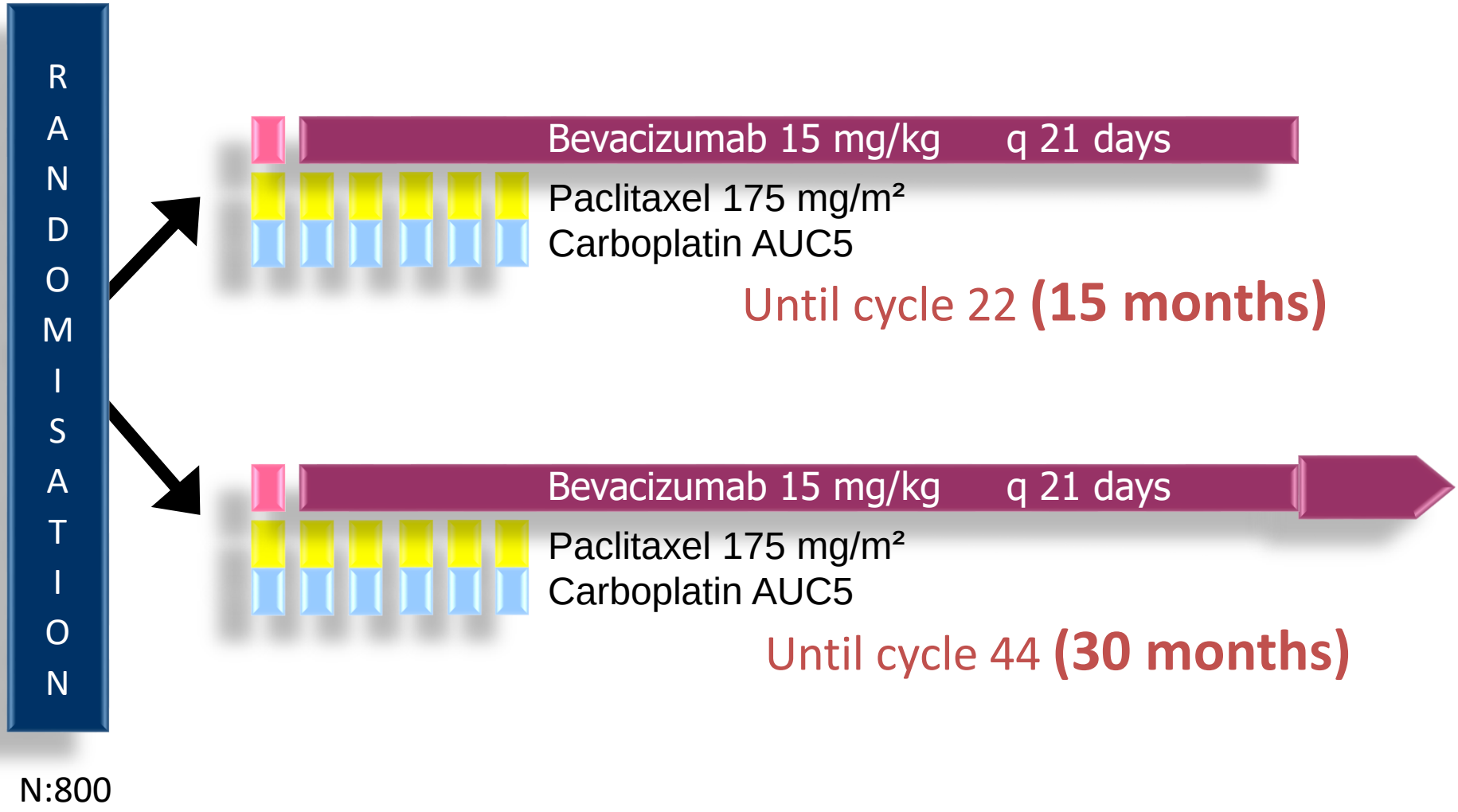
[2]Unpublished data, courtesy of MRC

Cumulative incidence of hypertension and proteinuria over time



BOOST trial

ENGOT-ov15/ AGO OVAR 17



N:800

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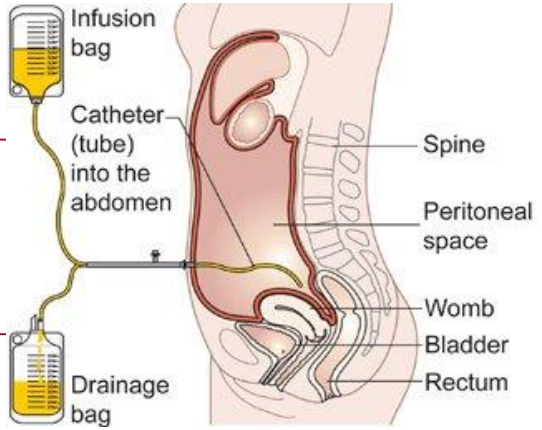
US: GOG 252

IP with BEV

Japan: iPocc

IP carboplatin vs IV

Intraperitoneal?



Canada: NCIC- CTG OV.21

IP carboplatin after interval debulking surgery

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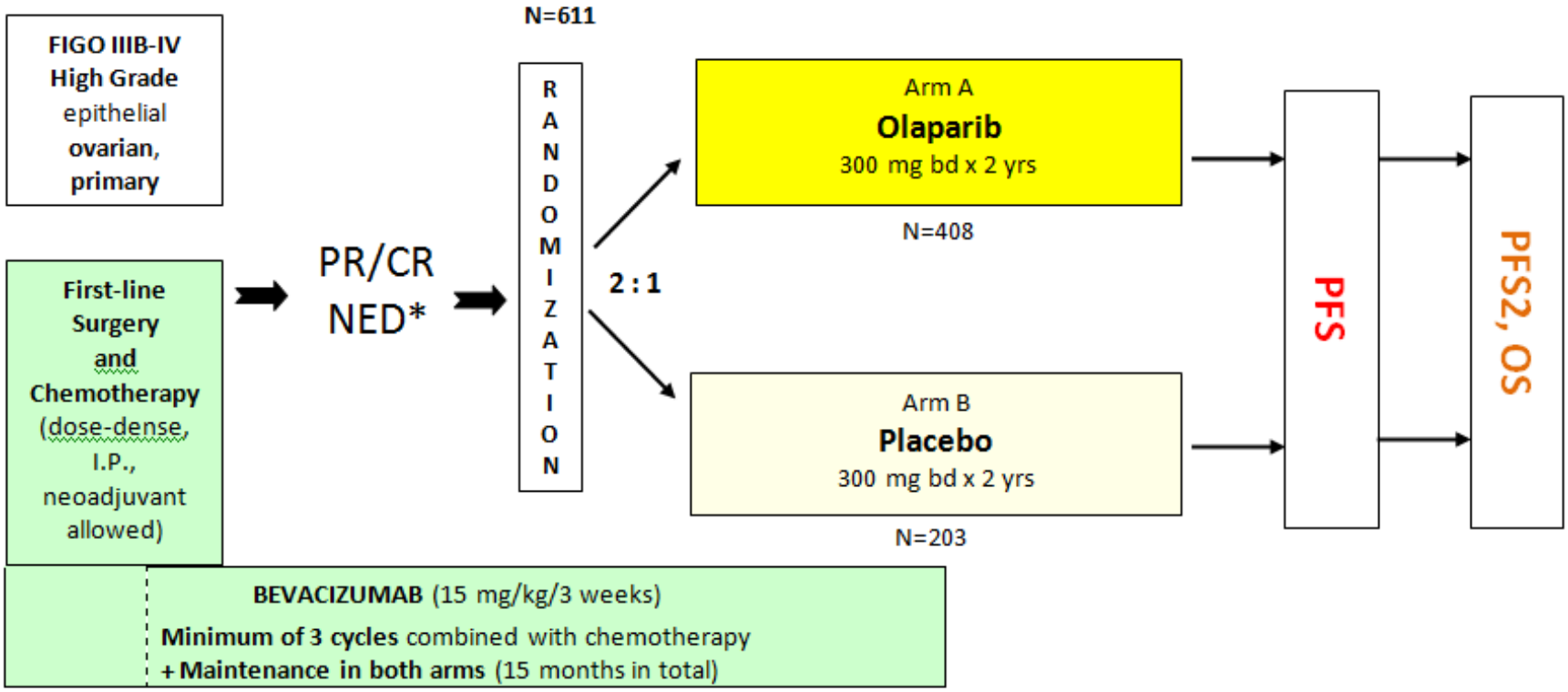
PAOLA 1


FIGO IIIB-IV
High Grade
epithelial
ovarian,
primary
First-line
Surgery
and
Chemotherapy
(dose-dense,
I.P.,
neoadjuvant
allowed)
PR/CR
NED*
N=611
RANDOMIZATION
2 : 1
Arm A
Olaparib
300 mg bd x 2 yrs
N=408
Arm B
Placebo
300 mg bd x 2 yrs
N=203
PFS
PFS2, OS
BEVACIZUMAB (15 mg/kg/3 weeks)
Minimum of 3 cycles combined with chemotherapy
+ Maintenance in both arms (15 months in total)

Multitargeted Therapy: Agents in Phase II/III Development

Agent	Target	Phase
Nintedanib	VEGFR + PDGFR + FGFR	III
Pazopanib	VEGFR + PDFGR + c-kit	III
Cediranib	VEGFR + PDGFR + FGFR + c-kit	III
Sunitinib	VEGFR + PDGFR + c-kit	II
Sorafenib	VEGFR + PDGFR + FGFR Flt-3 + c-kit + b-Raf	II
Vandetanib	VEGFR + EGFR	II
Motesanib	VEGFR + PDFGR + c-kit	II

- Small molecules
- Oral
- None are pure VEGFR inhibitors

Conclusions

- **BEV has proven benefit in first-line of advanced ovarian cancer.**
- **No advantage to deliver weekly paclitaxel schedule with BEV**
- **A longer duration of BEV may improve PFS without substantially compromising safety as suggested in ROSIA– to be confirmed in a comparative phase III trial**
  - **BOOST trial (NCT01462890): Prospective comparison of BEV 15 mg/kg for 15 vs 30 months both with carboplatin + paclitaxel**
- **Pending question:**

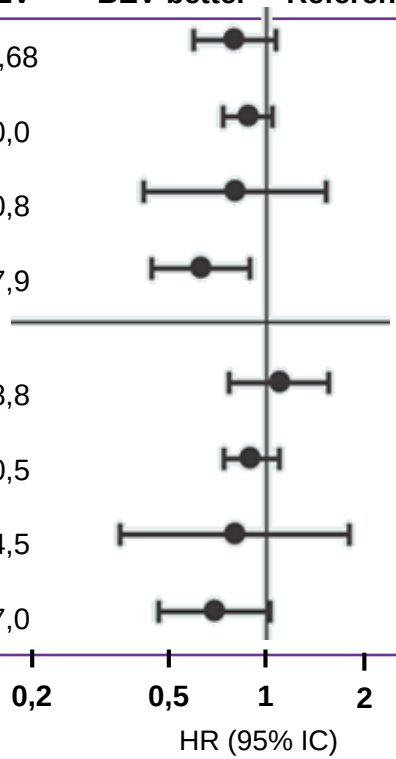
  Bev with IP? Bev with anti-Parp?

Back up slides

Subset analysis

Stage IIIB-IV according to residue

	Stage and residue	No. events/ patients (%)	Restricted mean Moyenne restreinte, mos				HR (95% IC)
			Reference	BEV	Reference	BEV	BEV better Reference better
PFS	**IIIB/IIIC 0 cm**	193/368 (52)	20,9	28,5	25,8	28,68	0,77 (0,58-1,02)
	IIIB/IIIC >0 cm	472/591 (80)	12,4	17,2	17,6	20,0	0,85 (0,71-1,01)
	IV 0 cm	35/43 (81)	13,0	19,0	17,8	20,8	0,88 (0,45-1,72)
	IV >0 cm	133/158 (84)	9,6	13,2	13,0	17,9	0,63 (0,45-0,89)
OS	**IIIB/IIIC 0 cm**	129/368 (35)	NA	NA	49,8	48,8	1,09 (0,77-1,53)
	IIIB/IIIC >0 cm	384/591 (65)	39,4	41,1	38,7	40,5	0,90 (0,74-1,10)
	IV 0 cm	25/43 (58)	41,6	49,2	40,1	44,5	0,80 (0,36-1,76)
	IV >0 cm	104/158 (66)	26,3	36,8	31,0	37,0	0,69 (0,47-1,02)



Gonzalez Martin A. *et al*. ASCO® 2015

PFS according to ‘MRC’ risk status and stage

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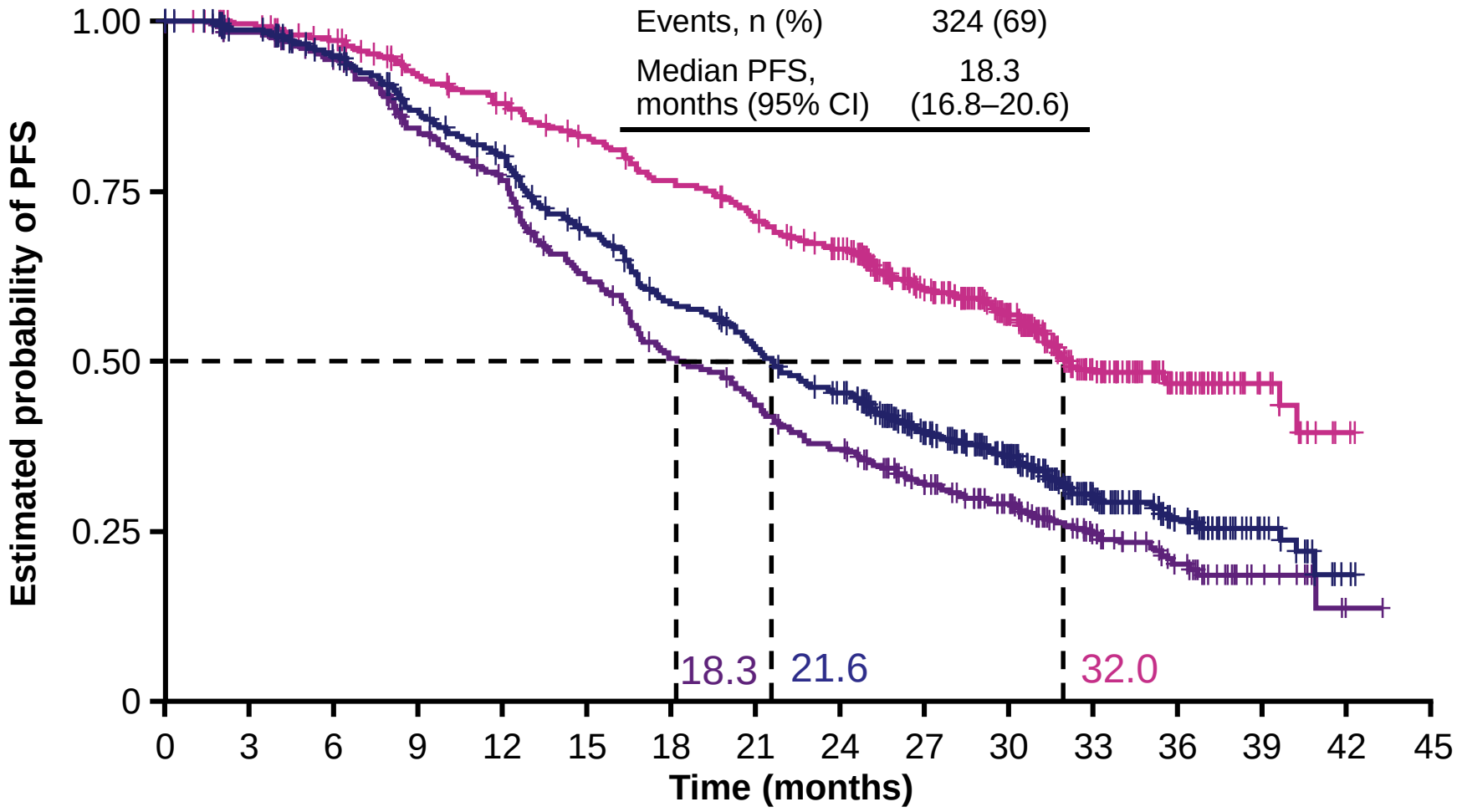


[a]FIGO stage III and >1 cm residual disease or any FIGO stage IV or no debulking surgery

Summary of grade ≥3 AEs of special interest (N=1021)

Patients (%)	Grade 3	Grade 4	Grade 5	Grade ≥3
Any grade ≥3 AE of special interest	**39.6**	**13.6**	**0.6**	**53.8**
Neutropenia and associated complications	18.2	11.0	0.1	29.3
Febrile neutropenia	2.3	0.6	0.1	2.9
Hypertension	24.1	0.6	0	24.7
Thrombocytopenia	8.1	1.7	0	9.8
Proteinuria	3.8	0	0	3.8
Thromboembolic events	1.9	0.8	0.3	2.9
GI perforation[a]	0.9	0.4	0.1	1.4
Bleeding	0.5	0.1	0.2	0.8
Wound-healing complication	0.4	0	0	0.4
Fistula/abscess	0.3	0.1	0	0.4

[a]Roche BEV basket terms, comprising: GI perforation (0.4%), abdominal abscess (0.1%), anal abscess (0.1%), anal fistula (0.1%), colonic abscess (0.1%), intestinal perforation (0.1%), jejunal perforation (0.1%), large intestine perforation (0.1%), perineal abscess (0.1%), peritoneal abscess (0.1%), peritonitis (0.1%)

Grade ≥3 AEs of special interest with first onset before vs after 22 cycles

Patients (%)	Cycles 0–22 (N=1021)	Cycle 23 onwards (N=528)
Any grade ≥3 AE of special interest	**50.9**	**12.9**
Neutropenia and associated complications	29.3	0
Hypertension	21.8	9.5
Thrombocytopenia	9.8	0
Proteinuria	2.8	2.3
Thromboembolic events	2.6	0.6
GI perforation	1.3	0.2
Fistula/abscess	0.4	0

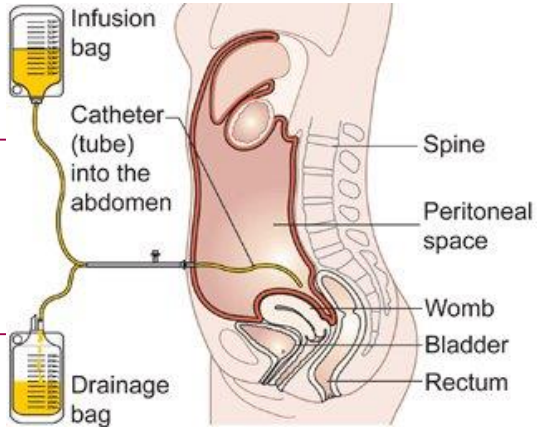
US: GOG 252

IP with BEV

Japan: iPocc

IP carboplatin vs IV

Intraperitoneal?



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